Sex Differences in Human Biological Aging

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This study aims to clarify sex differences in human biological aging and to explore the gender gaps in health and longevity. Eighty-six men and 93 women who received a 2-day routine health checkup for 6–7 years beginning in 1992 at the Kyoto Red Cross Hospital were selected. Five candidate biomarkers of aging (forced expiratory volume in 1.0 second per square of height [FEV₁/Ht²], systolic blood pressure [SBP], red blood cells [RBC], albumin [ALBU], and blood urea nitrogen [BUN]) were selected from 29 physiological variables. Individual biological ages (BAS) were estimated from these five biomarkers by a principal component model. From the investigation of the longitudinal changes of individual BAS, it was suggested that (i) the rate of aging showed a rapid increase, and (ii) women had relatively lower functional capabilities compared with men, but the rate of aging was slower than that of men, suggesting that these differences might present both disadvantages and advantages for women with regard to health and longevity.

Key Words: Biological age—Sex difference—Adult.

In developed nations, women tend to live longer than men and have notably lower death rates than men at all ages (1–3). The Japanese have the highest life expectancy at birth (78.6 years for men and 85.6 years for women in 2005) in the world. The sex difference in the average life span of the Japanese is almost 7 years. In addition, the numbers of Japanese centenarians in 2003 were 3159 men and 17,402 women (4). The number of centenarian women is approximately 5.5 times that of men. These figures suggest that women are biologically superior to men. However, it is also a well-known fact that women suffer from higher levels of morbidity than men (5,6).

As to possible reasons for the sex differences in longevity, it is, at present, considered that intrinsic differences based on genes, sex hormones, and reproductive physiology confer differential risks of morbidity (5,7,8). Besides these substantial factors, extrinsic factors such as lifestyle, health habits, exercise, nutrition, and the like may also have a connection with sex difference in biological vigor as potential moderators. At present, there is no single model that accounts adequately for group-level sex differences and for individual variability within each sex group (9). Manton and colleagues (10) suggested a need for more detailed biological models to represent the age dependency of human mortality as well as gender differences in that dependence. However, it is still not clear what factors might associate with sex differences in health and longevity. Is there any fundamental difference in the normal aging process that gives women an advantage?

To clarify this matter, we must have enough information about sex differences in human biological aging. The purpose of this study is to clarify sex differences in human biological aging, in terms of biological age as estimated by statistical means, and also to explore the biological aging superiority of women for health and longevity.

METHODS

Participants

Among about 25,000 Japanese adult men and women who received a routine health checkup from 1992 through 1998 at the Kyoto Second Red Cross Hospital, 86 adult men and 93 adult women who received a 2-day routine health checkup once a year (April to May) successively for 7 years from 1992 through 1998 were randomly selected as participants. Their past and present health status, work history, social and dietary habits, and so on, were determined from the medical questionnaire. Written informed consent was obtained from all participants.

Most of the participants were judged as healthy based on clinical criteria for normality as set by the Japanese Red Cross Hospital. These criteria have been described in more detail elsewhere (11). However, several elderly men and women with hypertension, diabetes, and/or hyperlipemia tendencies were included in the participants group. Most participants resided in Kyoto City. The male participants’ occupations were: managers (13%), salesmen (21%), researchers and engineers (6%), storekeepers (12%), teachers (6%), unemployed (19%), and various others (23%). The female participants’ occupations were housewives (33%), company employees (19%), public officials (13%), unemployed (10%), and various others (25%). The age range of participants in several age cohorts at the beginning of this study were from 31 to 77 years (with a mean age of 54.1 years) for men and from 31 to 77 years (with a mean age of 55.3 years) for women. An analysis of these mean ages by Student t test did not detect a significant difference (t(df = 1238) = 1.73, p < .077), which implies similar age populations. The number of participants by sex and age groups and their physical characteristics are given in Table 1.
Test Items and Procedure
The 2-day health examination consisted of more than 60 test items, including anthropometric measurements, cardiovascular and respiratory functions, and physical and chemical properties of blood and urine. Excluding the results of tests expressed by binary variables, and considering the relationship of the results of these tests with the aging process, the following 29 items tested during the routine checkups were assessed in the current study.

Results of cardiorespiratory function test: (1) forced vital capacity per square of height (FVC/Ht², L/m²); (2) forced expiratory volume in 1.0 second per square of height (FEV1/Ht², L/m²); (3) systolic blood pressure (SBP, mmHg); (4) diastolic blood pressure (DBP, mmHg);

Results of hematology assays: (5) white blood cell count (WBC, 10²/mm³); (6) red blood cell count (RBC, 10⁴/mm³); (7) hemoglobin concentration (HB, g/dL); (8) hematocrit (HCT, %); (9) mean corpuscular volume (MCV, fL); (10) mean corpuscular hemoglobin (MCH, pg); (11) mean corpuscular hemoglobin concentration (MCHC, %);

Results of biochemical assay of serum: (12) total protein (TPRO, g/dL); (13) albumin (ALBU, g/dL); (14) globulin (GROB, g/dL); (15) ratio of albumin to globulin (A/G ratio); (16) total bilirubin (TBILI, mg/dL); (17) alkaline phosphatase (ALK, IU/L); (18) γ-glutamyl transpeptidase (GTP, IU/L); (19) glutamate oxaloacetate transaminase (GOT, IU/L); (20) glutamic pyruvic transaminase (GPT, IU/L); (21) lactic dehydrogenase (LDH, IU/L); (22) blood urea nitrogen (BUN, mg/dL); (23) creatine (CREAT, mg/dL); (24) uric acid (URIC, mg/dL); (25) calcium (CALC, mg/dL); (26) total cholesterol (TC, mg/dL); (27) triglyceride (TG, mg/dL); (28) high-density lipoprotein cholesterol (HDLC, mg/dL); and (29) blood glucose (GLU, mg/dL).

Of the above-mentioned tests, pulmonary function (FVC and FEV₁) was measured using an electric spirometer (System-9; Minato Co. Ltd., Osaka, Japan) three times while standing, and the best record was used. Reproducibility was judged by the criteria of the American Thoracic Society cited by Ferris (12). In this analysis, FVC and FEV₁ were divided by the square of height (H²) to remove the effects of body size as suggested by Dockery and colleagues (13). Blood pressure (SBP and DBP) was measured manually using a sphygmomanometer after a 10-minute rest in a sitting position. Standard hematology and blood chemistry assays were performed at the Medical Laboratory of the Kyoto Red Cross Hospital. Biochemical measurements of heparinized blood were carried out using a Hitachi Automatic Analyzer (Model-7150; Tokyo, Japan). The hematological measurements were made on a Sysmex Automatic Blood Analyzer (E-4000; Tokyo, Japan).

Statistical Analysis
For systematic and logical selection of biomarkers of aging, the following step-wise methods were used: (i) cross-sectional analysis; (ii) longitudinal analysis; (iii) stability analysis; and (iv) assessment of redundancy. These criteria relate to both reliability and validity of candidate biomarkers of aging. In following this strategy, previous reports addressed potential biomarkers of aging in rhesus monkeys (14,15) and in healthy Japanese men (16). For all analyses, statistical significance was accepted as p < .05. All the computations were made with computer programs in the Statistical Package for Social Sciences (17).

RESULTS
Selection of Candidate Biomarkers of Aging
Table 2 provides the set of correlations used to guide the first three steps of the selection process to identify the candidate biomarkers of aging in men and women.

Step 1: Cross-sectional analysis.—To identify the degree of relationship between each variable and chronological age (CA), we first examined cross-sectional data for each year (from 1992 through 1998). Specifically, values for the 29 physiological, hematological, and blood chemistry variables were correlated with CA of each participant for each year across all age groups. Thus we produced seven correlations (Pearson product-moment) obtained for each of the 7 years were then averaged to obtain an estimate of the mean cross-sectional correlation with CA by using Fisher’s transformation of r to z and z to r. Based on this criterion, we identified the following 10 variables for further analysis:

Table 1. Age and Physical Characteristics of the Participants at Baseline Measurement

<table>
<thead>
<tr>
<th>Age Group (y)</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>60–69</th>
<th>70+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men Age (y), mean ± SD</td>
<td>35.9 ± 2.3</td>
<td>44.8 ± 2.9</td>
<td>54.2 ± 2.7</td>
<td>63.6 ± 2.8</td>
<td>73.3 ± 2.8</td>
</tr>
<tr>
<td>Height (m), mean ± SD</td>
<td>1.71 ± 0.04</td>
<td>1.68 ± 0.06</td>
<td>1.66 ± 0.05</td>
<td>1.64 ± 0.06</td>
<td>1.62 ± 0.06</td>
</tr>
<tr>
<td>Weight (kg), mean ± SD</td>
<td>66.9 ± 8.8</td>
<td>65.8 ± 6.6</td>
<td>65.9 ± 6.7</td>
<td>61.5 ± 7.4</td>
<td>60.3 ± 8.8</td>
</tr>
<tr>
<td>Participants (n)</td>
<td>17</td>
<td>26</td>
<td>18</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Women Age (y), mean ± SD</td>
<td>35.6 ± 2.4</td>
<td>44.7 ± 2.8</td>
<td>54.2 ± 3.2</td>
<td>64.0 ± 3.2</td>
<td>72.1 ± 2.1</td>
</tr>
<tr>
<td>Height (m), mean ± SD</td>
<td>1.57 ± 0.03</td>
<td>1.55 ± 0.06</td>
<td>1.53 ± 0.06</td>
<td>1.53 ± 0.05</td>
<td>1.49 ± 0.04</td>
</tr>
<tr>
<td>Weight (kg), mean ± SD</td>
<td>54.6 ± 5.3</td>
<td>53.4 ± 4.6</td>
<td>53.8 ± 7.9</td>
<td>55.0 ± 9.5</td>
<td>46.1 ± 7.4</td>
</tr>
<tr>
<td>Participants (n)</td>
<td>15</td>
<td>22</td>
<td>27</td>
<td>19</td>
<td>10</td>
</tr>
</tbody>
</table>

Note: SD = standard deviation.
Table 2. Summary of Correlation Coefficients Obtained From Cross-Sectional, Longitudinal, and Stability Analyses for Healthy Adult Men and Women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cross-Sectional Analysis</th>
<th>Longitudinal Analysis</th>
<th>Stability Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (N = 86)</td>
<td>Women (N = 93)</td>
<td>Men (N = 86)</td>
</tr>
<tr>
<td>1. FVC/Ht²</td>
<td>-0.518*</td>
<td>-0.589*</td>
<td>-0.508*</td>
</tr>
<tr>
<td>2. FEV₁/Ht²</td>
<td>-0.702*</td>
<td>-0.669*</td>
<td>-0.626*</td>
</tr>
<tr>
<td>3. SBP</td>
<td>0.358*</td>
<td>0.586*</td>
<td>0.580*</td>
</tr>
<tr>
<td>4. DBP</td>
<td>0.152</td>
<td>0.459*</td>
<td>0.405*</td>
</tr>
<tr>
<td>5. WBC</td>
<td>-0.051</td>
<td>-0.078</td>
<td>-0.115</td>
</tr>
<tr>
<td>6. RBC</td>
<td>-0.324*</td>
<td>-0.210*</td>
<td>-0.367*</td>
</tr>
<tr>
<td>7. Hemoglobin</td>
<td>-0.221</td>
<td>0.190</td>
<td>-0.229*</td>
</tr>
<tr>
<td>8. Hematocrit</td>
<td>-0.290*</td>
<td>0.167</td>
<td>-0.435*</td>
</tr>
<tr>
<td>9. MCV</td>
<td>0.205</td>
<td>0.432*</td>
<td>-0.139</td>
</tr>
<tr>
<td>10. MCH</td>
<td>0.159</td>
<td>0.398*</td>
<td>0.274*</td>
</tr>
<tr>
<td>11. MCHC</td>
<td>-0.024</td>
<td>0.145</td>
<td>0.422*</td>
</tr>
<tr>
<td>12. TPRO</td>
<td>-0.157</td>
<td>0.145</td>
<td>-0.019</td>
</tr>
<tr>
<td>13. Albumin</td>
<td>-0.441*</td>
<td>-0.250*</td>
<td>-0.310*</td>
</tr>
<tr>
<td>14. Globulin</td>
<td>0.175</td>
<td>0.304*</td>
<td>0.112</td>
</tr>
<tr>
<td>15. A/G ratio</td>
<td>-0.225*</td>
<td>-0.425*</td>
<td>-0.222*</td>
</tr>
<tr>
<td>16. TBILI</td>
<td>0.017</td>
<td>-0.237*</td>
<td>-0.041</td>
</tr>
<tr>
<td>17. ALK</td>
<td>0.163</td>
<td>0.550*</td>
<td>-0.333*</td>
</tr>
<tr>
<td>18. GTP</td>
<td>-0.023</td>
<td>-0.002</td>
<td>-0.206</td>
</tr>
<tr>
<td>19. GOT</td>
<td>0.092</td>
<td>0.247*</td>
<td>0.101</td>
</tr>
<tr>
<td>20. GPT</td>
<td>-0.061</td>
<td>0.019</td>
<td>-0.037</td>
</tr>
<tr>
<td>21. LDH</td>
<td>0.187</td>
<td>0.560*</td>
<td>-0.245*</td>
</tr>
<tr>
<td>22. BUN</td>
<td>0.358*</td>
<td>0.373*</td>
<td>0.251*</td>
</tr>
<tr>
<td>23. Creatine</td>
<td>0.269*</td>
<td>0.216*</td>
<td>0.181</td>
</tr>
<tr>
<td>24. Uric acid</td>
<td>-0.173</td>
<td>0.175</td>
<td>0.009*</td>
</tr>
<tr>
<td>25. Calcium</td>
<td>-0.176</td>
<td>0.362*</td>
<td>-0.173</td>
</tr>
<tr>
<td>26. Total cholesterol</td>
<td>0.122</td>
<td>0.195</td>
<td>-0.165</td>
</tr>
<tr>
<td>27. Triglyceride</td>
<td>-0.121</td>
<td>0.187</td>
<td>0.003</td>
</tr>
<tr>
<td>28. HDL-C</td>
<td>0.127</td>
<td>-0.009</td>
<td>0.179</td>
</tr>
<tr>
<td>29. Blood glucose</td>
<td>0.171</td>
<td>0.513*</td>
<td>0.129</td>
</tr>
</tbody>
</table>

Notes: *p < .01; †p < .05

FVC/Ht² = forced vital capacity per square of height; FEV₁/Ht², forced expiratory volume in 1.0 second per square of height; SBP = systolic blood pressure; DBP = diastolic blood pressure; WBC = white blood cell count; RBC = red blood cells; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; TPRO = total protein; A/G ratio = ratio of albumin to globulin; TBILI = total bilirubin; ALK = alkaline phosphatase; GTP = γ-glutamyl transpeptidase; GOT = glutamate oxaloacetate transaminase; GPT = glutamic pyruvic transaminase; LDH = lactate dehydrogenase; BUN = blood urea nitrogen; HDL-C = high-density lipoprotein cholesterol.

ALBU, GLOB, A/G ratio, TBILI, ALK, GOT, LDH, BUN, CREAT, CALC, and GLUC (p < .05) for women.

Step 2: Longitudinal analysis.—To identify the degree of genuine age-related “change” in each variable, we first transformed the measurement variable and CA of each participant across 7 years to z scores to standardize the scales. We then calculated correlations between CA and the values for each participant. Using Fisher transformation of the correlation coefficients, we first transposed the CA and the values for each variable across 7 years to reflect genuine age-related “change” in each variable. We then applied partial correlation analysis using CA as a covariate to control the effects of age. To calculate a mean value of the annual values for each variable. Specifically, correlations were calculated between the measurement value obtained for each of the variables and the corresponding measurement value of the succeeding year, for example, between 1992 and 1993, 1993 and 1994, and so on, across all ages within participants. Then we applied a partial correlational analysis using CA as a covariate to control the effects of age. To calculate a mean value of the partial correlation coefficients across the 7 years, we applied the Fisher transformation of r to z and z to r.

Step 3: Stability analysis.—Next we examined the degree of longitudinal stability of individual differences in all the variables. For this analysis, we evaluated the inter-year reliability of the annual values for each variable. Specifically, correlations were calculated between the measurement value obtained for each of the variables and the corresponding measurement value of the succeeding year, for example, between 1992 and 1993, 1993 and 1994, and so on, across all ages within participants. Then we applied a partial correlational analysis using CA as a covariate to control the effects of age. To calculate a mean value of the partial correlation coefficients across the 7 years, we applied the Fisher transformation of r to z and z to r.

Stability of measurement was observed in all the variables evaluated, ranging from 0.597 for GOT to 0.903 for MCV in men and from 0.524 for GPT to 0.892 for GTP in women. These results indicate a high degree of reliability for all the measurements made. Thus, we found that all eight variables emerging from Steps 1 and 2 showed statistically significant...
stability \((p < .01)\) with a correlation coefficient of \(>0.65\), except BUN.

Therefore, based on the statistical criteria of significant cross-sectional correlation with CA, significant longitudinal change with CA, and significant stability of individual differences, seven variables—FVC/\(Ht^2\), FEV\(_1/\)\(Ht^2\), SBP, RBC, ALBU, A/G ratio, and BUN—were further assessed as candidate biomarkers of aging.

**Step 4: Assessment of redundancy**.—For the set of variables identified in the preceding step, a correlation matrix was generated for all participants to examine their interrelationships and to identify possible redundant variables (Tables 3 and 4). A priori we had planned to eliminate from further analysis those variables that appeared to be redundant, i.e., from the same system (FVC/\(Ht^2\) and FEV\(_1/\)\(Ht^2\); and ALBU and A/G ratio). These variables showed a high correlation with each other, i.e., the correlation between FVC/\(Ht^2\) and FEV\(_1/\)\(Ht^2\) was 0.849 for men and 0.924 for women, and the correlation between ALBU and A/G ratio was 0.619 for men and 0.622 for women. Therefore, we selected FEV\(_1/\)\(Ht^2\) instead of FVC/\(Ht^2\), and ALBU instead of A/G ratio because these two variables showed much higher degrees of correlation in the other analyses than those of FVC/\(Ht^2\) and A/G ratio in longitudinal analysis, possibly reflecting the rate of aging. Thus, through this statistical screening process, we identified the following five candidate biomarkers of aging for use in constructing an index of biological age: SBP, FEV\(_1/\)\(Ht^2\), RBC, ALBU, and BUN.

**Principal Component Analysis**
A principal component analysis (PCA) was applied to the five candidate biomarkers of aging identified by the above criteria. This analysis was conducted to determine the structure of covariance. For the first analysis, CA was included to confirm the relationship between age and the principal component identified. For the second analysis, CA was excluded to ascertain whether the relationships of the candidate biomarkers to principal components would hold without the influence of CA.

The results of the first analysis indicated that in both sexes two major principal components with corresponding Eigenvalues \(>1.0\) were identified according to convention (18). The results of these analyses are shown in Table 5. About 60% of the total variance was accounted for by the two principal components. Along with CA, all the candidate biomarkers of aging showed significant loading onto the first principal component, which explained 42.2% for men and 38.2% for women of the total variance. Therefore, the first principal component appeared to be a major age factor. Results from the second analysis presented in Table 6 revealed that all the candidate biomarkers maintained their significant factor loadings onto the first principal component even when CA was eliminated. Moreover, this component continued to account for a high degree of the total variance (37.6% for men and 32.82% for women). From these results, we deduced that the five variables—the so-called FEV\(_1/\)\(Ht^2\), SBP, RBC, ALBU, and BUN—represented an underlying factor that might reflect processes of biological aging.

**Constructing Biological Age Score**
Because the five candidate biomarkers of aging were considered to measure underlying biological aging processes that were related statistically, we proceeded to combine them into a multivariate index, designated as a biological age score (BAS). To calculate individual BAS,
each test score for an individual was first standardized and then summed across tests in a weighted manner using the coefficients of the factor scores obtained in the PCA. In this procedure we reduced the equation used to calculate individual BAS to a simple equation as follows:

Men’s equation: \[ \text{BAS} = -2.288 \text{FEV}_1/H^2 + 0.018 \text{SBP} - 0.0086 \text{RBC} - 1.619 \text{ALBU} + 0.068 \text{BUN} + 9.48 \]

Women’s equation: \[ \text{BAS} = -3.289 \text{FEV}_1/H^2 + 0.033 \text{SBP} - 0.0093 \text{RBC} - 1.081 \text{ALBU} + 0.08 \text{BUN} + 6.08 \]

Individual BAS values for 86 adult men based on 7-year longitudinal data were calculated using the men’s equation. Figure 1 displays the scattergram of the BAS onto CA for all male participants. In the cross-sectional analysis based on 7 years of longitudinal data (data points = 602), individual BAS values were scattered relatively symmetrically above and below the regression line. The correlation coefficient between BAS and CA was 0.73 (\( p < .01 \)), and the standard error of the estimate (SEE) was 0.68.

In addition, individual BAS values for 93 adult women based on 6- to 7-year longitudinal data were calculated using the women’s equation (data points = 638). Figure 2 displays the scattergram of the BAS onto CA for all female participants. Individual BAS values were scattered relatively symmetrically above and below the regression line, as in the case of men. The correlation coefficient between BAS and CA was 0.72 (\( p < .01 \)), and the SEE was 0.76.

To clarify the relative importance of each biomarker to the estimation of BAS, the percentage contribution of each physiological variable to the variance of BAS was calculated using the following formula:

\[ \left( \frac{a_j^2}{\sum a_j^2} \right) \times 100 \quad (j = 1, 2, \ldots, p), \]

where \( a_j \) is a vector of the factor loadings of the first principal component and \( p \) is the number of variables. These results are illustrated in Figure 3. The highest percentage of contribution to the variance of the BAS was found in \( \text{FEV}_1/H^2 \) (35.9% for men and 37.3% for women). The next highest percentage of contribution was found in ALBU (26.3% for men) and in SBP (23.8% for women).

**Sex Differences in the BAS**

To clarify the sex differences in biological aging, we sought to compare the age-related changes of the BAS between the sexes. Thus, the BAS of 93 healthy adult women were calculated using the healthy men’s equation devised in this study, and they were overlaid on the scattergram of men’s BAS in Figure 1. The result of this analysis is shown in Figure 4. The BAS of women were relatively scattered above the regression line of the BAS for men. However, the slope of the regression line of the BAS onto CA for women was a little gentler than that of men. An analysis of these slopes by Student’s \( t \) test detected a significant difference (\( t(df = 1238) = 6.11, p < .001 \)). This result suggests that the rate of aging in women is a little slower than that of men. Figure 4 does not represent individual states of biological vigor inclusive of the rate of change in aging because of the cross-sectional data analyses. Thus, we calculated the regression line of the BAS onto CA for each woman across 6–7 years. Figure 5 shows the scattergram of men’s results. Figure 6 shows the scattergram of women’s results. In these figures, individual estimates of
BAS were eliminated to avoid a complex configuration. Only the regression lines were plotted. In the present study, we considered the slopes of these regression lines as aging rates. The trend of these regression lines with advancing age seems to follow an exponential curve. Thus, all the participants were divided into three age groups: young adult group (age < 45 years); middle-age group (45 ≤ age < 65 years); and older group (age ≥ 65 years). Mean slopes were calculated by age groups in both sexes. Young adult groups were 0.11 for men and 0.10 for women. Middle-aged groups were 0.13 for men and 0.08 for women. Older groups were 0.21 for men and 0.15 for women. The mean of the slopes calculated from the data for all participants by both sexes were 0.14 for men and 0.10 for women, and men's mean slope was a little higher than that of women. The difference of mean slopes between men and women was statistically significant at the 1% level ($t(df = 177) = 3.66$). In addition, the differences between mean slopes for age and gender groups in two-way analysis of variance detected a significant difference at the 1% level ($F$ value = 10.5 for gender, $F$ value = 13.9 for age group). From these and the above-mentioned results, we can deduce that women have relatively lower biological vigor compared with men, but the rate of aging is slower than that of men.

**DISCUSSION**

The possible sex differences in the biological risks have been examined to shed some light on the well-documented gender gaps for health and longevity. It is said that the longevity differences between both sexes are derived from the genetic process of sex determination, and also health differences result from gender differences in lifestyles including smoking, alcohol consumption, and exposure to risks such as occupational hazards and violence (19). At present, it is still not clear what major biological properties of an individual determine his or her lifelong health status and longevity. This study was conducted to clarify sex differences in human biological aging, and also to explore the gender gaps for health and longevity.

The maximum life span in humans appears to be the same for both sexes—about 115 years. This means that our
species’ upper age limit may be set by genetic limits locked into our genes (6). However, the age of death in humans will be mainly determined by the processes of aging, rather than by any accident of fate. Most of us will not experience our centenaries, even under the best of circumstances (20). The term "longevity" used in the present study was defined as not the maximum life span, but the life span based on natural death resulting from an aging process. Cutler (21) suggested that the health maintenance and longevity of an individual are determined by both maximum reserve capacity and aging rate of physiological functions. Different individuals have genetically determined differences in their peak functional capacities. If an individual ages at the same rate as another, his or her peak functional capacity may be potentially important in governing lifelong physical health. However, it has not yet been clarified whether there are sex differences in the physiological determinants of longevity.

Biological aging is defined as a process or group of processes that originate from a progressive decrement in viability and increment in vulnerability of the organ systems with the passage of time (22–24). From this definition, we can estimate that the individual differences to be seen in estimated biological ages reflect the degree of the biological vigor of individuals. In the present study, biological vigor was considered as an organism’s capacity to realize all functions essential to life. Five variables that are usable in both men and women (FEV\(_1\)/Ht\(^2\), SBP, RBC, ALBU, and BUN) were selected as candidate biomarkers of aging, and we combined them into a multivariate index, designated as a BAS. Manton and colleagues (10) used two of the five variables (FEV\(_1\)/Ht\(^2\) and SBP) to establish a model for sex differences in mortality. Especially, the mean of vital capacity index (VCI) for men and women declines to age 100, and then rises because mortality increases exponentially with age. Then, VCI must be nearly optimal with the passage of time (22–24). From the facts described above, this concept, of both biological aging rate and the extent of maximum reserve capacity. This figure suggests that, although women prototypically have less physical strength/health than men at their peak in early adulthood, the rate of decline across their remaining life span is lower than that of their male counterparts. Furthermore, women cross a theoretical "threshold" of vulnerability to terminal decline and death later than men, explaining the greater average longevity of women.

Figure 6. Relationship between biological age score (BAS) and chronological age by a longitudinal analysis in 93 healthy adult women. Individual scores of BAS were eliminated to avoid a very complex configuration. Only the regression lines for BAS with age were plotted.

Figure 7. Biological determinants of longevity and morbidity. Individual longevity might be determined by the rate of biological aging, and individual morbidity might be determined by biological vigor, which was measured by the extent of maximum reserve capacity. This figure suggests that, although women prototypically have less physical strength/health than men at their peak in early adulthood, the rate of decline across their remaining life span is lower than that of their male counterparts. Furthermore, women cross a theoretical "threshold" of vulnerability to terminal decline and death later than men, explaining the greater average longevity of women.

The BAS values of 93 healthy adult women were calculated using the men’s equation devised in this study, and compared with those of men. As is evident from Figure 4, most women’s BAS were scattered above the men’s regression line of the BAS on the CA. However, the slope of the regression line of BAS for women was a little gentler than that of the men (\(p < .001\)). These results were found in a cross-sectional study. A cross-sectional study based on data obtained at any one point in time cannot indicate the age changes directly (26). Thus we calculated the regression lines of the BAS onto the CA for each person across 6–7 years for both sexes. Detailed analyses of the longitudinal changes of the BAS in both sexes revealed that the mean slope of the regression lines for women was significantly lower than that of men (0.10 for women and 0.14 for men). The rate of aging in men was 1.4-fold higher than that in adult women. The rates at which men and women age are relatively slower until 65 years of age. After 65, their rates of aging rapidly advance (0.15 for women and 0.21 for men), following an exponential curve. From these results, we can deduce that women may possess relatively lower functional capabilities than men, but will age at slower aging rates than will men. This statement is well in accordance with Cutler’s hypothesis for the physiological determinants of longevity (21). However, although he considered that different individuals have different peaks of physiological capacity but age in this capacity at similar rates, the aging rate in the present analysis did not progress uniformly among all persons. The biological age of participants older than 65 years showed a tendency to converge in a constant course with aging. From the facts described above, this concept, of both biological aging rate and the extent of maximum biological vigor being potentially important in governing lifelong physiological health and longevity, is hypothetically illustrated in Figure 7. Namely,
although women prototypically have less physical strength/functional capacity (so-called biological vigor) than men at their peak in early adulthood, the rate of decline across their remaining life span is lower than that of their male counterparts. Furthermore, women cross a theoretical “threshold” of vulnerability to terminal decline and death later than men, explaining the greater average longevity of women.

For biological risks for health and longevity, intrinsic differences are based on genes, sex hormones, and reproductive physiology (7,8). However, these genotypic characteristics were not measured in the current study. We still know little about the biological reasons for the longevity and morbidity gender gap. Although the functional losses that occur in our vital systems as we age are normal events, they do increase our vulnerability to diseases. Therefore, we need to prevent a premature early aging phenomenon. Most biomedical research is directed toward resolving causes of death; the normal age changes that occurred before death simply increased the vulnerability of the deceased to whatever was written on the death certificate (6). In cases of older people, the increase in vulnerability resulting from the normal aging processes increases the danger of the death. Therefore, the higher aging rate of men may underlie their disadvantage for longevity. Short and colleagues (27) suggested that an alternative measure to longevity was the rate of aging. The rate of aging is the inverse of the life span, which reflects the vulnerability of an individual to death from normal aging processes. However, as pointed out by Hayflick (6), women’s greater longevity is accompanied by a higher incidence of many nonfatal diseases such as rheumatoid arthritis, hypertension, hearing impairments, and osteoporosis. These results might support the well-known paradox that men are more likely to die than women, but that women suffer from higher levels of morbidity than men (28–30).

The relative importance of each biomarker of aging to the estimation of BAS is, in a sense, expected to play an important role in determining one’s sex difference in biological vigor. The highest percentage contribution to the variance of BAS for women was found in \( \text{FEV}_1/\text{Ht}^2 \) (37.3%), and the next highest percentage contribution was found in SBP (23.8%). For men, the highest percentage contribution to the variance of BAS was found in \( \text{FEV}_1/\text{Ht}^2 \) (35.9%), and the next highest percentage contribution was found in ALBU (26.3%). The amount of variance that is occupied by these two variables exceeded 60% of the total variance for both sexes. The variables that showed most remarkable gender differences were SBP and ALBU; women showed 10.3% higher relative importance of SBP than men, whereas men showed 14.5% higher relative importance of ALBU than women. This gender difference would arise from biological factors based on genes and reproductive physiology, but we cannot fully explain the detailed reasons from the current analysis.

From the facts described above, we may conclude that women have relatively lower functional capabilities compared with men, but the rate of aging is slower than that of men, suggesting that these differences might cause a disadvantage or an advantage of women for health and longevity. From the current analysis, we still know little about the biological reasons for the life expectancy and morbidity gender gap. This study has some limitations concerning sample size and the choice of variables to study. After pathology was screened out, the end samples became 86 men and 93 women. In addition, the data set is highly selective and ends with the oldest individual at 77 years of age. Therefore, the applicability of biomarkers developed can only be used in narrowly defined subsets. Moreover, we need to add certain other biochemical indices in this model to clarify gender differences in longevity, for instance, hormonal and cardiovascular physiological indices. We further need to acknowledge the lack of information regarding mental health, cognitive function, personality, social stereotypes, and gender role behavior, which are related to gender differences in health. Further analyses including these factors will be necessary in the future.

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